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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,881	03/22/2004	Ibert C. Wells	800812-0005	9725

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,881	WELLS, IBERT C.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3, and 19 have been amended.

Claims 2 and 7-18 have been cancelled.

Claims 20—30 were previously cancelled.

Claims 1, 3-6, and 19 are pending and under examination in this Office action.

Response to Arguments

Applicant is thanked for the amendments to the specification to update the status of priority claims and to correct minor spelling errors.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

The rejection for omitting essential method steps has been withdrawn due to Applicant's amendment of claims, cancellation of claims, and persuasive arguments found on pages 8-9 of the response files March 7, 2005.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-6 and 19 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons of record set fort in the Office action mailed October 6, 2004.

The rejection set fort in the Office action mailed October 6, 2004 indicated that Applicant was enabled for detecting a lower than normal level of a tachykinin peptide in a body fluid being associated with essential hypertension but was not enabled for the detection of a lower level of a tachykinin peptide in a body fluid being associated with type 2 diabetes or preeclampsia. Applicant has narrowed the scope of the claims so that they now only read on the disease preeclampsia and has argued that the instant claims are fully enabled.

Applicant's arguments filed March 7, 2005 have been fully considered but they are not persuasive. Applicant's first argument found on pages 9 and 10 of the reply is that Applicant has demonstrated that the levels of the peptides of SEQ ID NOs:1, 2, and 4 correlate with the magnesium binding defect because administration of said peptides corrects the magnesium binding defect, and that the specification reports the discovery of an association of preeclampsia with the magnesium binding defect. In fact, the specification specifically teaches that the magnesium binding defect is at least a

contributory cause of preeclampsia (see particularly the last sentence of paragraph 54, said paragraph spanning pages 20 and 21 of the specification). Therefore, Applicant argues that the levels of these peptides correlate with preeclampsia.

This is not persuasive because as was indicated in the Office action mailed October 6, 2004 no measurement of peptide levels were ever performed using samples from patients with preeclampsia, or from patients suffering any of the disorders disclosed as being associated with the magnesium binding defect (i.e. hypertension and type 2 diabetes). The demonstration by Applicant that administration of the peptides of SEQ ID NOs:1 and 2 to red blood cells reverses the magnesium binding defect does not demonstrate that measuring the levels of these peptides in a bodily fluid, such as blood, is indicative of the magnesium binding defect since Applicant has not shown that a deficit of the peptides of SEQ ID NOs:1, 2, and 4 **causes** the magnesium binding defect. Since Applicant has not demonstrated or asserted a causal relationship, Applicant is invited to provide evidence demonstrating that measured peptide levels actually correlate with the presence of the magnesium binding defect. As stated in the Office action of October 6, 2004, this evidence is not present in the specification, and the specification does not provide a working example for the measurement of these peptides from a body fluid.

The Office action mailed October 6, 2004 also cited the work of Page et al. which demonstrates that the level of neurokinin B (which comprises SEQ ID NO:4 (FVGLM)) increases in women who have preeclampsia, and as such it is not clear that the finding

of a decreased amount of the recited peptides, as is required by the claims, would be indicative of preeclampsia.

Applicant's has amended the claims to replace the "comprising" language with "consisting of", and argues that it is the detection of tachykinin breakdown products (i.e. the peptides of SEQ ID NOs:1, 2, and 4) that are indicative of the magnesium binding defect, not the detection of the full length tachykinin peptides. The examiner acknowledges that the art closest to Applicant, that of Page et al., teaches that the detectable level of full-length neurokinin B increases with preeclampsia and is silent as to the levels of peptides consisting of SEQ ID NOs:1, 2, and 4. As such, it possible that detection of lower levels of the peptides of SEQ ID NOs:1, 2, and 4 is correlated with preeclampsia, but as indicated above, Applicant has not demonstrated this correlation. Applicant is invited to provide actual evidence demonstrating their claimed invention is contrary to that which is taught by Page et al.

Further, it is noted that the claims 1 and 3-6 are drawn to a method of assessing a predisposition to develop preeclampsia during pregnancy. As such, the intended patient population for this screening assay is pregnant women who do not have preeclampsia. The specification provides no examples demonstrating the measurement of the peptides of SEQ ID NOs:1, 2, and 4 in pregnant women, and then monitoring said women over the course of the pregnancy to determine if the measured levels of the peptides of SEQ ID NOs:1, 2, and 4 are associated with an increased risk of developing preeclampsia at a later time. Note that a predisposition does not need to indicate that an individual must develop preeclampsia, but it does need to indicate at a minimum that

it is more likely than not that this individual will develop preeclampsia at a later date. Detection of the peptides of SEQ ID NOs:1, 2, and 4 are not recognized in the art as being predictive for the development of preeclampsia or as being a symptom or sign of preeclampsia that can be used for diagnosis as evidenced by the Merck Manual of Diagnosis and Therapy, 17th edition, which indicates that the etiology of preeclampsia is unknown and that symptoms recognized as useful in the diagnosis of preeclampsia include hypertension, edema, proteinuria (see pages 2057-2058). The same relationship holds for the detection of the magnesium binding defect and preeclampsia. As such, the teachings of the prior art indicate correlating the levels of the peptides of SEQ ID NOs:1, 2, and 4 with preeclampsia is unpredictable, as was indicated to Applicant in the Office action mailed October 6, 2004. Applicant is invited to provide evidence that the detection of lower levels of the peptides of SEQ ID NOs:1, 2 and 4 as compared to a normal control baseline level has predictive power concerning which patients will and will not develop preeclampsia.

Therefore, due to the lack of working examples in the specification correlating the detection of lower than normal levels of the peptides of SEQ ID NOs:1, 2, and 4 with preeclampsia, the recognition in the closest prior art that the levels of neurokinin B, a precursor to the peptide of SEQ ID NO:4, increase rather than decrease in preeclampsia, and the fact that the state of the art does not recognize the detection of the peptides of SEQ ID NOs:1, 2, and 4 with either a predisposition to developing preeclampsia or the diagnosis of preeclampsia, make the correlation between the detection of the peptides of SEQ ID NOs:1, 2, and 4 and the disease preeclampsia

unpredictable. As such, a person of skill in the art would be required to conduct additional research before performing the method of Applicant's claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. The rejection of claims 1, 7, 8, and 19 under 35 U.S.C. 102(b) as being anticipated by Faulhaber et al. (J. Cardiovascular Pharmacology, 1987, Vol. 10 (Suppl. 12): S172-S176, see entire document) has been withdrawn due to Applicant's cancellation of claims 7, 8, and 19, and the amendment of claim 1 to limit its scope. Claim 1 is now limited to preeclampsia, while the prior art of Faulhaber et al. anticipates the disease essential hypertension. Therefore, this rejection has been removed.

6. The rejection of claims 1, 7, 8, and 11 under 35 U.S.C. 102(b) as being anticipated by Mori et al. (Jpn. Heart J. 1993, 34:785-794, see entire document) has been obviated by the cancellation of claims 7, 8, and 11, and amendment of claim 1. Claim 1 now is limited to preeclampsia while the prior art of Mori et al. anticipate the disease salt-sensitive essential hypertension. Therefore, this rejection has been removed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Applicant's arguments, see pages 11 and 12, filed March 7, 2005, with respect to all rejections under 35 USC 103 have been fully considered and are persuasive. Specifically, Applicant's amendment of claim 1, and cancellation of the other claims that were rejected in paragraphs 12 and 13 of the Office action mailed November 6, 2004, limits the scope the claim to just preeclampsia. As such, the prior art of record no longer reads on the claimed invention. Therefore, the rejections of pending claim 1 under 35 USC 103 have been withdrawn.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

This rejection has been withdrawn due to Applicant's amendment to the claims to limit the instant claims to preeclampsia. Neither US Patent 6,372,440 nor the prior art teach preeclampsia as being a medical condition associated with the magnesium binding defect, and as such it would not have been obvious to use the methods of US Patent 6,372,440 to detect preeclampsia.

New Grounds of Rejection

The following new ground of rejection is necessitated by Applicant's amendment filed February 4, 2005.

9. Claims 1, 3-6, and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of measuring peptides comprising SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:4, or peptides consisting of SEQ ID NO:1 or SEQ ID NO:4, does not reasonably provide enablement for methods of measuring peptides consisting of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has claimed a method of measuring a peptide consisting of SEQ ID NOs:1, 2, or 4. Applicant has also disclosed general guidelines that are well known in the art for performing standard curves, developing ELISA and RIA assays, and for producing both polyclonal and monoclonal antibodies (see particularly page 22, paragraph 57 to page 38, paragraph 110). The specification does not appear to disclose that such immunoassays assays were ever performed or that antibodies of the requisite binding specificity were ever generated.

Couraud et al. (J. Neurochemistry, 1987, 49:1708-1718) disclose the production and characterization of monoclonal antibodies and a polyclonal serum that bind SP using standard techniques (see entire document, particularly the Materials and Methods section, pages 1709-1711). Table 3 (page 1714) details the percent relative binding of the polyclonal antiserum and five monoclonals for SP, SP analogues substituted with alanine, fragments of SP, and other tachykinins. All of the monoclonal antibodies and

the polyclonal sera specifically recognize SP, a fragment of SP that corresponds to SEQ ID NO: 1 (listed as SP (7-11)), and neurokinins A and B. None of these antibodies demonstrate any reactivity toward the SP fragment that corresponds to SEQ ID NO: 2 (SP (8-11)). Couraud et al. note that the polyclonal sera shows a pattern of specificity similar to the monoclonal antibodies, indicating that the serum did not contain antibodies with markedly different specificities (page 1713, right column, end of the paragraph that started on page 1712).

Based upon the teachings of Couraud et al., it does not appear that an antibody that specifically binds a sequence consisting of SEQ ID NO: 2 can be made using standard art recognized techniques, but antibodies that specifically bind a sequence consisting of SEQ ID NO: 1 or 4 can be successfully produced. Applicant has not disclosed that an antibody that specifically binds a sequence consisting of SEQ ID NO: 2 has been made, nor has Applicant indicated any additional techniques in addition to those commonly known in the art that would be required to overcome the difficulty in generating an antibody that specifically binds a sequence consisting of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement set forth. Without additional guidance, it is not possible to practice the full breadth of Applicant's claims as an undue amount of experimentation would be required to make an antibody that specifically binds a sequence consisting of SEQ ID NO: 2.

10. No claims are allowable.

11. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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